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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,070	05/11/2006	Hoon Han	36470-231114	3303

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,070	HAN ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/30/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 30, 2009 that includes a response to the final office action dated October 30, 2008, has been entered. Claims 1 and 3 have been amended, and claims 4-8 newly added. No claims were cancelled. Claims 1-8 are pending in the application and under current examination.

Information Disclosure Statement

The information disclosure statement dated 1/30/2009 has not been fully considered, as indicated on Form PTO-SB/08A, because 37 CFR 1.98 (b)(5) requires that each publication listed in an information disclosure statement must be identified by publisher, author (if any), title, relevant pages of the publication, date, and place of publication.

New Claim Objection

Claim 8 is newly objected to because of the following informalities: The claim recites "C29 in the third line". The correct designation should be "CD29". Appropriate correction is required.

New Claim Rejection - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is unclear. The claim recites: "wherein the umbilical cord blood has a volume of more than 45 ml per unit". The limitation of more than 45 ml sets no upper limit and reads on an infinite number of milliliters. Thus, the metes and bounds of the claim remain undefined.

Response & Withdrawn Claim Rejections - 35 USC § 103

Claims 1-3 were rejected under 35 U.S.C. §103(a) as being unpatentable over Erices et al. (Br. J. Hematol. 109:235-242; 2000), in view of Nishikawa et al. (U.S. Patent Application Publication No.: 2004/0235160; effective filing date: Aug. 7, 2002), and further in view of Petaja et al. (J. Clin. Invest. 99:2655-2663; 1997), in the previous office actions dated April 14, 2008 and October 30, 2008. In view of Applicants' amendment of base claim 1, deleting language regarding anti-coagulant per unit volume of cord blood, the previous rejection is hereby withdrawn. The claims are however subject to new rejections over the prior art, as set forth below.

To the extent that Applicants' arguments are applicable to the new rejections, they are addressed as follows:

Applicants traverse the rejection, arguing that Erices et al. does not disclose or use a medium that includes Stem Cell Factor, GMCSF, G-CSF, IL-3 and IL-6. Applicants' arguments have been fully considered, but are not found persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The limitations regarding

additional culture additives and cytokines are provided by the secondary reference of Nishikawa et al.

Applicants argue that the art teaches that one would not expect to isolate MSCs from UCB and cite Mareschi et al. teaching that early fetal blood is rich in MSCs, but full term UCB is not. Such is not found persuasive, because, the cited reference acknowledges the presences of MSCs in pre-term UCBs, and the instant claims fail to limit the term or type of UCB claimed. Moreover, as previously indicated, Mareschi et al. qualify their statements, by indicating that Erices et al. recently identified mesenchymal progenitor cells in 25% of their UCB harvests, and that their results were obtained using a pool of different units of pre-term UCB, and probably, in such as a way as to enhance the rather low population of MSCs in pre-term UCB. Thus, highlighting differences between their methodology and that employed by Erices et al.

Applicants argue that Romanov et al. allege that Erices et al. may not have isolated MSCs. Again, such is not found persuasive, because the cited reference limited the isolation of MSCs from the subendothelial layer of umbilical cord veins, and none the less concluded that umbilical cord stroma may be considered an alternative source of MSCs, confirming the presence of MSCs in umbilical cord.

Applicants argue that Wexler et al. state that cord blood is not a reliable source of MSC, and that true MSCs are negative for CD34, CD45 and CD14. Such is not found persuasive, because, the same marker profile is disclosed by Erices et al. on page 239, Fig. 4.

Applicants argue that one skilled in the art would not be motivated to combine Nishikawa et al., which relates to HSCs, with Erices et al. Such is not found persuasive, because Applicants have selectively ignored the pertinent embodiments of Nishikawa et al. regarding Stromal or mesenchymal cells (see page 4), and Examples 5 teaching both mesenchymal and hematopoietic stem cell. A person of ordinary skill in the art would further be motivated to combine respective teachings of the references because Nishikawa et al. specifically describe isolation of mononuclear cell fractions following ficoll hypaque density gradient centrifugation of umbilical cord blood.

In sum, Applicants have failed to disqualify the Erices et al. reference and its teachings.

New Claim Rejections - 35 USC § 103

Claims 1-4, 6 and 7 are newly rejected under 35 U.S.C. §103(a) as being unpatentable over Erices et al. (Br. J. Hematol. 109:235-242; 2000), in view of Nishikawa et al. (U.S. Patent Application Publication No.: 2004/0235160; effective filing date: Aug. 7, 2002).

The claims embrace a method for isolating and culturing mesenchymal stem cells from umbilical cord blood comprising obtaining umbilical cord blood within 24 hours post partum, adding an anti-coagulant to said blood unit, diluting the resulting mixture 2-fold with α-MEM medium, centrifuging over Ficoll-Hypaque to harvest monocytes, and subjecting the monocytes to α-MEM medium containing glutamine, fetal bovine serum, antibiotics, anti-fungal agent amphotericin B, stem cell factor (SCF), granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), interleukin-3 (IL-3) and interleukin-6 (IL-6).

Erices et al. describe the harvest and preparation of mesenchymal progenitor cells from human umbilical cord blood (Title and Abstract). Specifically describing the harvest of cord blood from preterm and term deliveries by processing blood samples ≤ 24 hours after harvest, wherein the cord blood was drained into glass bottles containing 10 ml of M-199 culture medium containing heparin (an anti-coagulant). The diluted cord blood cells are further described as separated into low-density fraction on Hystopaque-1077® (Sigma; functional equivalent of Ficoll-Hypaque (Pharmacia); both having a specific gravity of 1.077 g/ml), to obtain mononuclear cells (i.e. monocytes), that were suspended into culture medium comprising α-MEM, fetal bovine serum and gentamycin sulfate (second column, p. 235 to second column, p. 236). The characterization of adherent primary culture mesenchymal cells are described in the second column, p. 238.

It should be noted that the fold-dilution of cord blood with medium, prior to gradient centrifugation can vary depending upon the volume of cord blood obtained and the volume of Ficoll-Hypaque to be centrifuged. Moreover, the medium for dilution of the cells prior to centrifugation may be M-199 or α-MEM, both disclosed by Erices et al.; that a person of ordinary skill in the art would regard as functional equivalents for the purposes of dilution. Thus,

the limitation of 2-fold dilution is obvious due to the requirements of the Ficoll-Hypaque density gradient.

While Erices et al. do not describe the inclusion of glutamine, cytokine growth factors or anti-fungal agent in their culture medium, the inclusion of such factors as a cocktail for mesenchymal cell culture was well known in the prior art.

Nishikawa et al. describe methods for culturing human mesenchymal stem cells and hematopoietic stem cells (Example 5, p. 8), including the isolation of human umbilical cord blood stem cells following the separation of mononuclear cells by density gradient centrifugation of heparinised umbilical cord blood overlaid on Ficoll-paque (Example 6, p. 8). Nishikawa et al. describe conditions for cell growth in medium supplemented with L-glutamine, antibiotics streptomycin and penicillin, amphotericin B (an antimicotic), SCF, G-CSF, IL-3 and IL-6 (¶ [0076], p. 9), that may additionally include GM-CSF (¶ [0032], p. 3); thus curing the deficiency of mesenchymal cell culture supplements in Erices et al.

As the methods described by Erices et al. and Nishikawa et al. are directed to the isolation of monocytes from umbilical cord blood treated with anti-coagulant, for culture and production of mesenchymal stem cells, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the instant invention to combine their respective teachings to include the culture supplements of Nishikawa et al., in the method of Erices et all, thus resulting in the method of instantly claimed invention. Therefore, an artisan of ordinary skill, having combined the elements of anti-coagulant treated umbilical cord blood and various mesenchymal cell culture supplements in the monocyte isolation and culture method of Erices et al. would have a reasonable expectation of success in producing mesenchymal stem cells via the instantly claimed method of isolating and culturing monocytes.

Claims 1, 5 and 8 are newly rejected under 35 U.S.C. §103(a) as being unpatentable over Erices et al. (Br. J. Hematol. 109:235-242; 2000), in view of Nishikawa et al. (U.S. Patent Application Publication No.: 2004/0235160; effective filing date: Aug. 7, 2002), as applied to

claims 1-4, 6 and 7 above, and further in view of Goodwin et al. (Biol. Blood Marrow Transplant. 7:581-588; 2001).

The claims embrace a method for isolating and culturing mesenchymal stem cells from umbilical cord blood that has volume of more than 45 ml per unit, comprising obtaining umbilical cord blood within 24 hours post partum, adding an anti-coagulant to said blood unit, centrifuging to harvest monocytes, and subjecting the monocytes to α-MEM medium containing stem cell factor (SCF), granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), interleukin-3 (IL-3) and interleukin-6 (IL-6), and wherein the isolated mesenchymal stem cells are negative for CD14, CD34, CD45 and positive for SH2, SH3, CD29, CD44, CD90 and CD166 markers.

Erices et al. describe the harvest and preparation of mesenchymal progenitor cells from human umbilical cord blood (Title and Abstract). Specifically describing the harvest of cord blood from preterm and term deliveries by processing blood samples ≤ 24 hours after harvest, wherein the cord blood was drained into glass bottles containing 10 ml of M-199 culture medium containing heparin (an anti-coagulant). The diluted cord blood cells are further described as separated into low-density fraction on Hystopaque-1077® (Sigma; functional equivalent of Ficoll-Hypaque (Pharmacia); both having a specific gravity of 1.077 g/ml), to obtain mononuclear cells (i.e. monocytes), that were suspended into culture medium comprising α-MEM, fetal bovine serum and gentamycin sulfate (second column, p. 235 to second column, p. 236). The resulting mesenchymal-like cells are described as expressing CD29, CD90, but did not express CD14, CD34 and CD45 (Fig. 4 and second column, p. 240).

Nishikawa et al. describe methods for culturing human mesenchymal stem cells and hematopoietic stem cells (Example 5, p. 8), including the isolation of human umbilical cord blood stem cells following the separation of mononuclear cells by density gradient centrifugation of heparinised umbilical cord blood overlaid on Ficoll-paque (Example 6, p. 8). Nishikawa et al. describe conditions for cell growth in medium supplemented with L-glutamine, antibiotics streptomycin and penicillin, amphotericin B (an antimicotic), SCF, G-CSF, IL-3 and IL-6 (¶ [0076], p. 9), that may additionally include GM-CSF (¶ [0032], p. 3).

While Erices et al. and Nishikawa et al. do not disclose the isolated mesenchymal stem cells as additionally positive for CD44 and CD166, such are properties inherent to the cells, as evidenced by Goodwin et al., describing the isolation of stromal cells from umbilical cord blood expressing CD29 and CD44 (Abstract), and weakly expressing CD166 (Figure 3 and Table on p. 585). Goodwin et al. describe the isolation of the cells from a 250-ml standard collection bag containing anticoagulant by fractionating mononuclear cells on Ficoll-Hypaque (first column, p. 582; limitation of claim 5).

As the methods described by Erices et al., Nishikawa et al. and Goodwin et al. are directed to the isolation of monocytes from umbilical cord blood treated with anti-coagulant, for culture and production of mesenchymal stem cells, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the instant invention to combine their respective teachings to isolate the cells from a volume of more than 45 ml per unit, thus resulting in the method of instantly claimed invention. Therefore, an artisan of ordinary skill, having combined the elements regarding anti-coagulant treated umbilical cord blood in the monocyte isolation and culture methods described would have a reasonable expectation of success in producing mesenchymal stem cells that express CD44 and CD166 markers, via the instantly claimed method of isolating and culturing monocytes.

Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent Application No: 10/579,071. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass a method of isolating and culturing mesenchymal stem cells from umbilical cord blood comprising the step of isolating the cells from a Ficoll-Hypaque monocyte fraction. The claims are considered obvious variants of each other because cryopreserved cord blood cells were known and routinely used in the art at the time of the claimed invention, and the CD133 marker is an inherent property of the isolated cells. In addition, Thus, to practice the invention of the instant application, it would have been *prima facie* obvious to utilize the cryopreserved umbilical cord blood of the '071 Application. Therefore, the '071 and instant Application claims are obvious variants of one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 1-8 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Examiner, Art Unit 1633